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EXAMINER	
CHONG, KIMBERLY	
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1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,176	RANA, TARIQ M.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/31/2007, 11/12/2007 and 12/5/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,19-28,30 and 33-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,19-28,30 and 33-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 10/31/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 07/26/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 05/03/2007, claims 14, 19-28, 30 and 33-44 are pending and currently under examination in the application.

Response to Declaration

The declaration filed on 11/12/2007 under 37 CFR 1.132 is sufficient to overcome the rejection of claims 14, 19-28, 30 and 33-44 based upon 35 U.S.C. 112,

first paragraph. The declaration provides adequate support for the claimed delivery agent consisting of a generation 4 dendrimer.

Information Disclosure Statement

The information disclosure statement filed 05/03/2007 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. The IDS was previously considered 07/23/2007 but is has come to the attention of the Examiner that the NPL documents listed as #2 and #3 do not have a date associated with the reference and therefore the references have not been considered. The remainder of the documents cited on the IDS has been considered by the examiner and signed copies have been placed in the file.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14, 19, 38, 39 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Szoka et al. (US Patent No. 5,661,025).

The instant claims are drawn to a delivery mixture comprising a 2 to 5 generation dendrimer mixed with a nucleic acid capable of mediating RNAi, wherein the nucleic acid is an RNA molecule, wherein the dendrimer is PAMAM and wherein the dendrimer is a generation 4 dendrimer.

Szoka et al. teach DNA, RNA and RNA:DNA hybrid molecules wherein the molecules are mixed with PAMAM dendrimers having generations 2 to 5 (see columns 9 and 10 and see Table 2) . Absent evidence to the contrary, the molecules taught by Szoka et al. are capable of mediating RNAi.

Thus, Szoka et al. anticipates claims 14, 19, 38, 39 and 43 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14, 19-28, 30 and 33-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al. (Clinical Cancer Research 2001), Tuschl et al. (cited on PTO Form 892 filed 08/23/05) and McManus et al. (cited on PTO Form 892 filed 08/23/05) Olejnik et al. (cited on PTO Form 892 filed 08/23/05) and Grigoriev et al.

(cited on PTO Form 892 filed 08/23/05) and evidenced by Milhem et al. (International Journal of Pharmceutics 2000, Vol. 197: 239-241).

The instant claims are drawn to a delivery mixture comprising a 2 to 5 generation dendrimer mixed with a nucleic acid capable of mediating RNAi, wherein the nucleic acid is an RNA molecule, wherein the RNA is a miRNA, a shRNA or a siRNA, wherein the siRNA comprises a sense and antisense strand complementary to a target mRNA sequence, wherein the sense and antisense strands are crosslinked, wherein the crosslink is psoralen, wherein the siRNA comprises a modification at the 3'OH terminus, wherein the modification is a photocleavable biotin, wherein the dendrimer is PAMAM, wherein the dendrimer is a generation 4 dendrimer, wherein the dendrimer to nucleic acid ration is as recited in claims 40-42 and wherein the siRNA is from 16-30, 23-32 or 21 nucleotides in length.

Sato et al. teach an antisense oligonucleotide mixed with a G4 dendrimer (see page 3607) wherein the G4 dendrimer is known as a PAMAM starburst generation 4 dendrimer as evidenced by Milhem et al. (see page 240, column 1). Sato et al. teach the antisense oligonucleotide to dendrimer ratio used was 1:1 or 1:100 (see page 3607 and 3611). Sato et al. teach the mixture comprising the antisense oligonucleotide and G4 dendrimer had a broad biodistribution in tissues of the animal compared to the antisense oligonucleotide not mixed with the G4 dendrimer (see page 3609 and Figure 3) and further efficient internalization into the cells (see page 3608). Sato et al. do not teach mixing a siRNA with a dendrimer, do not specifically teach the siRNA to dendrimer concentration at a ratio of between about 10 ug to 1 mg or 20 ug to 40 ug or

about 40 ug and do not teach incorporation of a photocleavable biotin or psoralen crosslinks.

Tuschl et al. teach siRNA molecules, 19-23 nucleotides in length comprising 3' 2 nucleotide overhangs that are capable of mediating RNAi wherein the nucleotides of the sense strand and antisense strand are complementary to the target gene (see page 6, lines 8-15 and Figure 14). Tuschl et al. teach siRNAs are efficient alternatives compared to antisense compounds for silencing gene expression. Likewise, McManus et al. teach shRNA and microRNA which are capable of mediating RNAi (see page 740).

Olejnik et al. teach oligonucleotides comprising photocleavable biotin (see page 362).

Grigoriev et al. teach incorporation of psoralens into oligonucleotide for formation of psoralen crosslinks (see Figure 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the delivery mixture comprising a dendrimer for delivering a siRNA instead of an antisense molecule. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate modifications such as photocleavable biotin and crosslinks using psoralens, into the siRNA.

One would have been motivated to make a delivery mixture comprising a dendrimer and a siRNA or a microRNA or shRNA instead of an antisense because Tuschl et al. and McManus et al. teach such nucleic acid compounds are more efficient than antisense for probing gene function and for inhibiting gene expression. In probing gene function and inhibition of gene expression, one of skill in the art would be

motivated to use the most efficient methodology for mediating RNAi efficiently in cells, thereby allowing elucidation of gene function. Because siRNA is an inhibitory nucleic acid molecule, one would expect to encounter similar issues in delivery to cells as with antisense oligonucleotides and therefore one would be motivated to use a delivery mixture comprising a dendrimer because the goal for siRNA therapy is optimal delivery of the siRNA and enhanced cellular uptake by the cells.

Sato et al. teach in tumor bearing mice, a G4 dendrimer mixed with an antisense compound delivered significantly larger amounts of the antisense compared to the antisense compound without being mixed with a G4 dendrimer (see page 3610). Sato et al. do specifically teach an oligonucleotide to dendrimer concentration at a ratio of between about 10 ug to 1 mg or 20 ug to 40 ug or about 40 ug, but do teach various ratios of oligonucleotide to dendrimer ratio therefore demonstrating the routine nature of testing various ratios for optimization of the most efficient ratio for delivery and gene inhibition. Therefore because the use of dendrimers in a delivery mixture, as claimed by the instant invention, were known to add benefits to delivery of oligonucleotides molecules to cells, one would have been motivated to make a delivery mixture comprising siRNA and test various ranges for the optimal concentration.

One would have been further motivated to incorporate a photocleavable biotin modification at the end of the siRNA contained in the delivery mixture comprising a dendrimer because Olejnik et al. teach incorporation of a photocleavable biotin into a oligonucleotide provides a simple method for purification of oligonucleotides (see abstract). Additionally, Olejnik et al. teach incorporation of a photocleavable biotin

allows isolation of nucleic acids after synthesis and after cleavage of the biotin moiety, the functional nucleic acids can be used in further methods (see page 361). Further, one would have been motivated to incorporate psoralens, as taught by Grigoriev et al., into the siRNA contained in the delivery mixture to increase the target specificity of the siRNA to the target gene once the siRNA is delivered to cells. Grigoriev et al. teach addition of psoralen derivatives to oligonucleotides increase the antisense target affinity and half-life by crosslinking the antisense oligonucleotide to the target (see page 3501).

Finally, one would have a reasonable expectation of success at making a delivery mixture comprising a G4 dendrimer and a siRNA given Sato et al. teach efficient delivery of an antisense nucleic acid and given one would expect the siRNA nucleic acid molecule to be delivery similarly. Additionally, it is a matter of routine skill in the art to use the dendrimer and oligonucleotide at different concentrations to determine the effective ratio of dendrimer to oligonucleotide for efficient delivery into cells. Further, one would have had a reasonable expectation of success at incorporating a photocleavable biotin and psoralen crosslinks into the siRNA contained in the delivery mixture because Olejnik et al. teach synthesis of an oligonucleotide comprising a photocleavable biotin and teach efficient purification of the oligonucleotide and photocleavable of the biotin moiety and further Grigoriev et al. teach efficient inhibition of gene expression using cross linked nucleic acids.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 112

The rejection of claims 14, 19-28, 30 and 33-44 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to the declaration filed 11/12/2007 as explained above.

Re: Claim Rejections - 35 USC § 102

The rejection of claims 14, 20, 22-24 and 43 under 35 U.S.C. 102(e) as being anticipated by Frecht et al. (U.S. Patent No. 7,097,856) is maintained for the reasons of record in the Office action mailed 07/26/2007.

Applicant's arguments in the response filed 10/31/2007 are acknowledged but not found persuasive. Applicant states the Examiner acknowledged during an interview on 10/26/2007 that if the claims recited a mixture of two separate molecules, this would distinguish over Frecht et al. Applicant argues Frecht et al. does not anticipate the instant invention because Frecht et al. do not teach "a mixture of a dendrimer molecule and a nucleic acid molecule (i.e., mixture of two separate molecules)" and one of skill in the art would recognize that the claims provide for a mixture of separate molecules, when the claims are interpreted in view of the specification. Applicant points to support for limitation recited as "mixed with" in claim 14 on page 12 of the instant specification.

First to make the record clear, the Examiner never definitively stated that amending the claims to recite a mixture of two separate molecules would distinguish over Frecht et al. What was discussed in the interview was the interpretation of claim

by the Examiner and how Frecht et al. met the limitations of the instant claims given the claims were drawn to a delivery mixture (which is not defined in the instant specification) comprising a dendrimer and a nucleic acid and how this recitation did not exclude a dendrimer conjugated to a nucleic acid. Further, as stated in the interview summary of record, the term mixture was discussed and whether the dendrimer-oligonucleotide taught by Frecht et al. was a mixture. If Applicant's or Applicant's representative suggested any amendment to the claims during the interview, the Examiner would have considered this amendment but would have never indicated the amendment would be sufficient to overcome any prior art rejection of record without the claim amendments being properly submitted into the record and subsequently examined.

In response to Applicant's assertion the one of skill in the art would recognize that the instant invention provide for a mixture of two separate molecules in light of the specification, this line of argumentation is not convincing. The specification on page 12, as indicated by Applicant as providing support, states "The siRNAs of the invention can also be delivered by mixing with a delivery agent, e.g. a dendrimer." The term mixing is not further defined in the instant specification and the step of a siRNA mixed with a dendrimer does not exclude the step of conjugation. Moreover, on page 9 of the instant specification, the siRNA is described as having at its 3' terminus a dendrimer (see lines 10-13). Therefore, based on this description, a dendrimer can be conjugated to the 3' end of the siRNA.

Therefore, Frecht et al. anticipates the instant claims and the rejection of record is maintained.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 14, 19-20, 23-34 and 38-42 and 44 under 35 U.S.C. 103(a) as being unpatentable over Woolf (cited on PTO Form 892 filed 08/23/05), Olejnik et al. (cited on PTO Form 892 filed 08/23/05), Grigoriev et al. (cited on PTO Form 892 filed 08/23/05) and Yoo et al. (cited on PTO Form 892 filed 08/23/05) is withdrawn in response to Applicant's arguments and therefore a response to Applicant's arguments is moot.

The rejection of claims 14, 17-24 and 32-44 under 35 U.S.C. 103(a) as being unpatentable over Yoo et al. (cited on PTO Form 892 filed 08/23/05) in view of Hammond et al. (cited on PTO Form 892 filed 08/23/05), Tuschl et al. (cited on PTO Form 892 filed 08/23/05) and McManus et al. (cited on PTO Form 892 filed 08/23/05) is withdrawn in response to Applicant's arguments and therefore a response to Applicant's arguments is moot.

The rejection of record of claims 14, 17-24, 32-34 and 38-42 under 35 U.S.C. 103(a) as being unpatentable over Yoo et al. (PTO Form 892 filed 08/23/05) in view of Hammond et al. (Nature 2001, Vol. 2: 110-119), Tuschl et al. (WO 02/44321) and McManus et al. (Nature Review: Genetics 2002)) is withdrawn in response to Applicant's arguments and therefore a response to Applicant's arguments is moot.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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